REMARKS

Claims 1-35 were pending in the present application. Claims 29-32 and 35 were rejected under 35 U.S.C. § 102(a) and § 102(e); claims 1-35 were variously rejected under 35 U.S.C. § 112, first paragraph.

By virtue of this response, claims 7, 17, 26, 29-32 and 34-35 have been cancelled and claims 1, 10, 20 and 33 have been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification and, for example, at page 24, lines 19-22, page 26, lines 5-15 and in original claims 7, 17, 26, 29 and 34.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicant expressly reserves the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

Applicant has carefully considered the points raised in the Office Action and believes that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance. Reconsideration of the rejections contained in the Office Action is respectfully requested.

Drawings

The drawings were objected to in Paper No. 7 for reasons set forth in the PTO-948 attached thereto. Submitted herewith are corrected drawings.

Rejections under 35 U.S.C. § 102(a) and § 102(e)

Claims 29-32 and 35 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Krieg (1999, *J. Gene Med.*, 1:56-63) and under 35 U.S.C. § 102(e) as allegedly being anticipated by Krieg et al. (U.S. Pat. No. 6,218,371). Applicant respectfully traverses these rejections.

As outlined in the response to the Office Action filed October 9, 2002, neither Krieg nor Krieg et al. disclose a kit comprising a composition comprising an ISS-containing polynucleotide nor a kit that does not comprise a herpes simplex virus antigen. Neither Krieg nor Krieg et al. disclose administration of the composition to an individual infected with, exposed to or at risk of being exposed to herpes simplex virus. Neither Krieg nor Krieg et al. disclose the claimed kit with instructions which describe administration of the composition to an individual infected with, exposed to or at risk of being exposed to herpes simplex virus. Accordingly, as neither reference discloses each and every element of claims 29-32 and 35, neither reference anticipates the claimed invention.

However, solely in the interest of expediting prosecution, Applicant has herein canceled claims 29-32 and 35, making this rejection moot. In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(a) and § 102(e).

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-35 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention in scope with the claims. Applicant respectfully traverses this rejection.

The amended claims are directed to methods of preventing a symptom of, reducing severity of, and reducing recurrence of a symptom of herpes simplex virus infection in an individual comprising administering an ISS-containing polynucleotide composition in the

absence of administration of a herpes simplex virus antigen. In the claims, the ISS comprises the sequence 5'-C, G-3', the polynucleotide comprises a phosphate backbone modification and the individual is a mammal. The amended claims are also directed to a kit for use in ameliorating or preventing a symptom of herpes virus infection comprising a composition comprising a polynucleotide comprising particular ISS sequences and instructions for use, wherein the kit does not comprise a herpes simplex virus antigen.

The Examiner states that the specification is "enabling for a method of preventing symptoms of, reducing severity of or reducing recurrence of a symptom of herpes infection in mice and guinea pigs challenged with herpes virus, by administering the *phosphorothioate* polynucleotide comprising the immunostimulatory sequences set forth as SEQ ID NO: 1 and 9 to said mice and guinea pigs." The Examiner further states that the specification "does not reasonably provide enablement for a method of reducing the severity of a symptom of herpes virus infection in any individual or mammal comprising administering any sequence comprising 5'-C, G-3' sequence." Office Action, page 6, original emphasis.

As an initial matter, Applicant respectfully traverses this rejection of claims 29-35 for the reasons outlined herein. However, solely in the interest of expediting prosecution, claims 29-32 and 34-35 have been canceled and amended claim 33 is directed to a kit for use in ameliorating or preventing a symptom of herpes virus infection comprising a composition comprising a polynucleotide comprising SEQ ID NO: 1 or SEQ ID NO:9, wherein the polynucleotide comprises a phosphate backbone modification, and comprising instructions for administration to an individual where the individual is a mammal, wherein the kit does not comprise a herpes simplex virus antigen.

Also, Applicant respectfully submits that claimed methods comprising administration of polynucleotides without a phosphate backbone modification and claimed kits comprising a polynucleotide without a phosphate backbone modification are fully enabled by the specification. However, solely in the interest of expediting prosecution, the claims have been amended to recite that the polynucleotide comprises a phosphate backbone modification.

In support of the rejection, the Examiner cites Agrawal et al. (2002, *Trends Mol. Med.* 8:114-121, "Agrawal") and Hartmann et al. (2000, *J. Immunol.* 164:1617-1624, "Hartmann"), two references which describe "optimal" and "second generation" CpG DNA motifs. The Examiner states that comments in Agrawal "demonstrate the high degree of uncertainty in the art with regard to extending results obtained using ISS DNAs in one species to other species of mammals" and that Hartmann "teaches that use of phosphorothioate backbone, or some other means for protecting the ISS from nuclease degradation is required for *in vivo* clinical utility." Office Action, pages 8 and 9. In the rejection, the Examiner concludes that "it would require undue experimentation to practice the invention commensurate with the full scope of the claims." Office Action, page 10. Applicant respectfully disagrees with this basis for the rejection.

As noted above, a phosphate backbone limitation has been added to the polynucleotide of the pending claims. Thus, the claimed invention conforms with the Examiner's assertion regarding that particular aspect of Hartmann.

In studies to identify an optimal CpG motif, the cited references describe different degrees of responsiveness of cells from various mammalian species to 5'-C, G-3' containing oligonucleotides. As noted by the Examiner, Agrawal states that "[a]lthough the presence of an unmethylated CpG dinucleotide is essential for induction of immunostimulatory activity, the sequences flanking the CpG dinucleotide also play a role." Agrawal, page 114, right column. Agrawal also states that "[d]eletion of either C or G nucleotide in a CpG dinucleotide results in the absolute loss of immunostimulatory activity" and that "changes of the nucleotide sequences two bases away from the CpG dinucleotide on either side does not have significant influence on immunostimulatory activity." Agrawal, page 117, right column. Thus, Agrawal teaches that the 5'-C, G-3' dinucleotide is essential to immunostimulatory activity and that changes in the flanking sequences may or may not optimize activity of an immunostimulatory oligonucleotide.

The Examiner admits that the "level of skill in the relevant art is very high." Office Action, page 9. Indeed, Hartmann describes testing of more than 250 phosphorothioate oligonucleotides to identify the oligonucleotide with the highest activity in a variety of primate

cells. Applicant respectfully submits that, in view of the specification and that known in the art, it is well within the ability of a skilled artisan to vary sequences flanking the 5'-C, G-3' dinucleotide, if necessary, to generate an optimally active sequence.

The specification provides adequate guidance to enable one skilled in the art to make and use the claimed invention. Many examples of ISS for use in the invention and methods for their synthesis are provided, for example, on pages 24-34. Means of assessing the functional activity of the ISS-containing polynucleotides as claimed are provided, for example, on pages 38-40. The working examples in the specification (pages 42-48) exemplify ISS-containing polynucleotides with activity as claimed. Such extensive disclosure provides adequate guidance such that a skilled artisan would be able to practice the invention without undue experimentation.

Applicant respectfully submits that the test for enablement is not whether a certain amount of experimentation is required to practice an invention, but rather whether the amount of experimentation is "undue." As the court held in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), the test for enablement does not rest merely on the quantity of experimentation that would be required to practice an invention, "since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Applicant has provided an adequate description and data in the form of working examples that shows how to assess the claimed activity of the ISS-containing polynucleotide.

The court in *In re Wands* found that the enablement requirement was satisfied by a "disclosure [that] provides considerable direction and guidance on how to practice [the] invention and presents working examples," in view of the fact that "[t]here was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." *Id.* at 740. With respect to the present invention, polynucleotides containing immunostimulatory sequences were known in the art as demonstrated, for example, by the many references cited on pages 4-6 as well as by Agrawal and Hartmann. As outlined above, the specification provides considerable guidance as to how to

identify and make ISS-containing polynucleotides for use in the invention and how to assess the activity of ISS-containing polynucleotides in the claimed methods. Thus, following the reasoning in the *In re Wands* decision, the disclosure is adequate to enable the invention as claimed.

Thus, the specification provides adequate guidance pertaining how to make and use the claimed immunomodulatory polynucleotides. Accordingly, the pending claims are in compliance with the enablement requirements.

Claims 1-28 were rejected under 35 U.S.C. § 112, first paragraph, because the specification is allegedly not enabling for a method and compositions wherein the composition is administered outside of the affected area. Applicant respectfully traverses this rejection.

The Examiner asserts that the "specification only describes, in specific terms, embodiments of the invention wherein the CpG oligonucleotides are administered topically at the site of inoculation with herpes virus (see especially Examples 1 and 2)." Office Action, page 12. Applicant respectfully disagrees with this assertion.

The specification exemplifies administration of ISS-containing polynucleotides locally and systemically. The specification exemplifies local administration of the ISS-containing polynucleotides through topical administration at the site of the herpes lesion in Example 1, page 42 through page 44, line 9, and in Example 2, page 46, line 4, through page 47, line 5. The specification also exemplifies systemic administration of the ISS-containing polynucleotides through intraperitoneal injection in Example 2, page 45, line 9, through page 46, line 2. At page 45, lines 9-24, the specification describes ISS therapy that is administered through injections. Applicant's Declaration, provided herewith, states that in "the procedures described at page 45, line 9, to page 46, line 2, of the specification, the ISS therapy referred to as "ISS injections" was administration of ISS-containing polynucleotides though intraperitoneal injections." Van Nest Declaration, paragraph 3.

Applicant respectfully submits that the specification exemplifies that administration of ISS-containing polynucleotides both locally and systemically is effective for in treating a symptom of herpes infection.

Thus, the specification provides adequate guidance to teach one skilled in the art how to make and use the claimed invention. Accordingly, the pending claims are in compliance with the enablement requirement.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicant has, by way of the amendments and remarks presented herein, addressed all issues that were raised in the outstanding Office Action. Applicant respectfully contends that this Amendment has overcome the rejections and that the pending claims are in condition for allowance. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001100.

Respectfully submitted,

Dated: March 24, 2003 By: _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please enter the following amendments without prejudice or disclaimer.

In the Claims:

Please cancel claims 7, 17, 26, 29-32 and 34-35 without prejudice or disclaimer.

Please amend claims 1, 10, 20 and 33 as follows.

1. (Amended) A method for preventing a symptom of herpes simplex virus infection in an individual who has been exposed to herpes simplex virus, comprising administering a composition comprising a polynucleotide comprising an immunostimulatory sequence (ISS) to said individual, wherein the ISS comprises the sequence 5'-C, G-3', wherein the polynucleotide comprises a phosphate backbone modification, wherein a herpes simplex virus antigen is not administered in conjunction with administration of said composition, wherein the individual is a mammal and wherein said composition is administered in an amount sufficient to prevent a symptom of herpes simplex virus infection.

10. (Amended) A method of reducing severity of a symptom of herpes simplex virus infection in an individual infected with herpes simplex virus, comprising administering a composition comprising a polynucleotide comprising an immunostimulatory sequence (ISS) to said individual, wherein the ISS comprises the sequence 5'-C, G-3', wherein the polynucleotide comprises a phosphate backbone modification, wherein a herpes simplex virus antigen is not administered in conjunction with administration of said composition, wherein the individual is a mammal and wherein said composition is administered in an amount sufficient to reduce severity of a symptom of herpes simplex virus infection.

20. (Amended) A method of reducing recurrence of a symptom of herpes simplex virus infection in an individual infected with herpes simplex virus, comprising administering a composition comprising a polynucleotide comprising an immunostimulatory sequence (ISS) to said individual, wherein the ISS comprises the sequence 5'-C, G-3', wherein the polynucleotide comprises a phosphate backbone modification, wherein a herpes simplex virus antigen is not administered in conjunction with administration of said composition, wherein the individual is a mammal and wherein said composition is administered in an amount sufficient to reduce recurrence of a symptom of herpes simplex virus infection.

33. (Amended) [The kit of claim 29] A kit for use in ameliorating or preventing a symptom of herpes simplex virus infection in an individual infected with, exposed to or at risk of being exposed to herpes simplex virus, comprising:

a composition comprising a polynucleotide comprising an immunostimulatory sequence (ISS), wherein the ISS comprises the sequence 5'–TGACTGTGAACGTTCGAGATGA–3' (SEQ ID NO:1) or the sequence 5'-TCGTCGAACGTTCGTTAACGTTCG-3' (SEQ ID NO:9), wherein the polynucleotide comprises a phosphate backbone modification and wherein said kit does not comprise a herpes simplex virus antigen; and

instructions for administration of said composition to an individual infected with, exposed to or at risk of being exposed to herpes simplex virus, wherein the individual is a mammal.